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10/551,374	03/30/2006	Andrew S. Janoff	532552001100	3088

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EXAMINER
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HIBBERT, CATHERINE S

ART UNIT	PAPER NUMBER
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1636

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03/17/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/551,374	<b>Applicant(s)</b> JANOFF ET AL.	
	<b>Examiner</b> Catherine S. Hibbert	<b>Art Unit</b> 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 13 June 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,5,6,10,11,15 and 22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,5,6,10,11,15 and 22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 September 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1/10/2006</u> .   | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

This is the First Office Action on the Merits of US Application 10/551,374, filed 30 March 2006, which is a National stage entry of PCT/US2004/010388, filed 2 April 2004, which claims priority to 60/460,223 filed 2 April 2003, 60/495,394 filed 15 August 2003, and 60/496,180 filed 18 August, 2003. Claims 2-4, 7-9, 12-14, 16-21, and 23-25 are cancelled. Claims 1, 5, 6, 10, 11, 15, and 22 are pending and under examination in this action.

### ***Election/Restrictions***

Applicant's election with traverse of Group I in the reply filed on 13 June 2008 is acknowledged. The traversal is on the ground(s) that Applicants submit by amending Claims 5 and 10 (both from Group II) to now depend from Claim 1, that Applicants essentially argue to combine Groups I and II. Specifically, Applicants point out that Claim 22 of Group I also includes the step of preparing the actual pharmaceutical composition and that thus Applicants believe that presently amended Claims 1 and Claim 5 in combination are of essentially the same invention group as Claim 22. This is found persuasive and therefore Group I now contains amended Claims 1, 5, 6, 10, 11, 15, and 22.

The requirement is still deemed proper and is therefore made FINAL.

### ***Oath/Declaration***

It is noted that the inventive entity on the Oath/Declaration and ADS consists of the inventors Janoff, Mayer and Bally whereas the inventive entity listed on the Bibliographic Data Sheet consists of Janoff and Mayer.

***Specification***

The use of the trademark Herceptin (e.g. page 1) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5, 6, 10, 11, 15, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The independent Claim 1 recites the limitation "the concentration range" in lines 12-13. There is insufficient antecedent basis for this limitation in the claim because there is no antecedent reference to "a concentration range" or to "a concentration" of any kind, or to the ratio of agents being measured with respect to "a concentration".

Claims 5, 6, 10, 11 and 15 are indefinite insofar as they depend from Claim 1.

The independent Claim 22 recites the limitation "the concentration range" in lines 16-17. There is insufficient antecedent basis for this limitation in the claim because there is no antecedent reference to "a concentration range" or to "a concentration" of any kind, or to the ratio of agents being measured with respect to "a concentration".

Additionally, Claim 22 recites the limitation "the molecular phenotype of said patient's diseased cells" in line 4. There is insufficient antecedent basis for this limitation in the claim as there is not previous mention of a molecular phenotype of the patient's cells and it is unclear how many parameters must be characterized to determine "the molecular phenotype" of the patient's cells.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**Claims 1 is rejected** under 35 U.S.C. 102(b) as being anticipated by Osaki et al in "Alteration of drug chemosensitivity caused by the adenovirus-mediated transfer of the wild-type p53 gene in human lung cancer cells" (Cancer Gene Therapy, 2000, Vol. 7: pages 300-307; made of record in the IDS).

Claim 1 is directed to a method for determining a patient-specific, non-antagonistic ratio of two or more therapeutic agents comprising: (i) providing diseased

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cells obtained from a patient; (ii) characterizing a molecular phenotype of said diseased cells; (iii) matching the molecular phenotype of said diseased cells with the molecular phenotype of a cultured cell line; (iv) providing at least a first and a second therapeutic agent; and (v) assaying the first therapeutic agent in combination with the second therapeutic agent at various ratios *in vitro* on said cultured cell lines to determine a ratio of said first and second therapeutic agents that exhibits a non-antagonistic biological effect on said cultured cell lines, whereby said ratio is identified as a patient-specific, non-antagonistic ratio, wherein said non-antagonistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cultured cells are affected in said *in vitro* assay.

Osaki et al teach a method to determine the beneficial (i.e. non-antagonistic) ratios of the combination of the therapeutic anti-cancer agents including the adenovirus-mediated transfer of the wild-type (wt) p53 gene and several different cancer drugs (e.g. p. 301, Figure 1 and legend). For example, the graph in Figure 1 shows supra-additive (i.e. synergistic ratios), and additive ratios, both of which are considered to be non-antagonistic (e.g. p. 301, right column). Osaki et al discloses the optimization of the combination of anticancer agents by studying the effect of various combinations of agents and at various concentrations of agents on two cell lines: a human pulmonary squamous cell carcinoma cell line and a human pulmonary large cell carcinoma cell line (p. 300, ¶ 2). These cell lines are correlates to a specific patient molecular phenotype of lacking wt p53 (e.g. p. 300, ¶ 1). Osaki et al teach assaying a first therapeutic agent in combination with a second therapeutic agent at various ratios *in vitro* on these

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cultured cell lines and conclude that certain combinations could be used for treating non-small cell lung cancer in patients (see abstract). In addition, Osaki et al shows in the graphs in Figure 3 (page 303) that a non-antagonistic effect is exhibited over at least 20% of a concentration range such that 20-80% of the cultured cells are affected in said *in vitro* assay.

**Claim 1 is rejected** under 35 U.S.C. 102(b) as being anticipated by Bepler et al in "Additive and Differential Biological Activity of  $\alpha$ -Interferon A Difluoromethylornithine And Their Combination on Established Human Lung Cancer Cell Lines " (Cancer Research, 1986, Vol. 46, No. 7:pages 3413-3419; made of record in the IDS).

Claim 1 is as described above.

Bepler et al teach methods of testing drugs or combinations of drugs on cells which are representative of a specific patients phenotype. For example, Bepler et al disclose studying the effect of a combination of IFN- $\alpha$ A and DL- $\alpha$ -difluoromethylornithin (DFMO) on human lung cancer cell line variants. Bepler et al showed that an inhibitory effect for one of the drugs was very different for the classic and variant phenotypes, respectively, but for the other drug no such distinction was observed. These cells read on patient-specific phenotypes because it was concluded that only patients suffering from the variant phenotype small cell lung cancer would benefit from a treatment regimen combining the two drugs (see abstract and p. 3417, left hand column, last paragraph to the right-hand column, last paragraph). In addition, Bepler et al shows in the graphs in Figure 3 that an additive effect of the drug combination is exhibited over at least 20% of a concentration range such that 20-80% of the cultured cells are affected in the *in vitro* assay (Fig. 3 and legend p. 3415).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:



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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 5, 6, 10, 11 and 22** are rejected under 35 U.S.C. 103(a) as being unpatentable over Bepler et al or Osaki et al, both as applied to Claim 1 above, and further in view of Saxon et al in "Liposomal Anticancer Drugs as Agents to be Used in Combination with other Anticancer Agents: Studies on a Liposomal Formulation with Two Encapsulated Drugs" (Journal of Liposome Research, Vol. 9, No. 4, 1999, pages 507-522, entire document).

Claim 1 is as described above and is taught by Bepler et al for the reasons above and is also taught by Osaki et al for the reasons above. In addition, Bepler et al contemplate providing their optimized drug combination (ratio) *in vivo* to mouse models "to confirm these results before entering into clinical trials" (e.g. abstract) and Osaki et al contemplate using their optimized drug combination for preparation of a pharmaceutical to treat cancer patients lacking wt p53 (e.g. p. 300, ¶ 1).

Claims 5, 10 and 22 are directed to a method of providing a pharmaceutical preparation individualized to a particular patient comprising the method steps of Claim 1 and a step of mixing a first composition comprising a first delivery vehicle associated with a first therapeutic agent with a second composition comprising a second delivery vehicle stably associated with a second therapeutic agent wherein the pharmacokinetics of the delivery vehicles in the first and second compositions are coordinated, wherein the non-antagonistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cultured cells are affected in said *in vitro* assay. Claim 6 specifies within Claim 5 that the combination of said first and second composition occurs immediately prior to use. Claim 11 specifies within Claim 10 that the first therapeutic agent is stably associated with a first delivery vehicle and the second therapeutic agent is stably associated with a second delivery vehicle.

While Bepler et al teach a patient-specific, additive (non-antagonistic) ratio of the drugs IFNs and DFMO to be used to in a pharmaceutical preparation, and Osaki et al teach a patient-specific, synergistic and additive therapeutic agent combination to be used in a pharmaceutical preparation, neither Bepler et al nor Osaki et al explicitly teach that the combination drugs are "stably associated" with a first and second "delivery vehicle".

It would have been obvious for one of ordinary skill in the art at the time of Applicants invention to prepare a pharmaceutical composition of an optimized drug combination using stably associated delivery vehicles to administer the drug combination as shown in Saxon et al because using stably associated delivery vehicles for drug administration was conventional at the time of Applicants invention (e.g. Saxon et al, abstract).

One of ordinary skill in the art would have been motivated to combine the delivery vehicles of Saxon with the optimized drug combination composition of Bepler et al because Bepler et al contemplate delivering their combination to animal models and then to human clinical trials and Saxon et al describe successful modes of delivery for combination drugs for pharmaceutical use.

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the use of the stably associated delivery vehicles for the purpose of delivering combination drug therapy was routinely practiced at the time of Applicants invention (e.g. Saxon et al).

In view of the foregoing, the method of claims 5, 6, 10, 11 and 22, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a).

**Claim 15 is rejected** under 35 U.S.C. 103(a) as being unpatentable over Bepler et al or Osaki et al, in view of Saxon et al, as applied to Claims 1 and 10 above, and further in view of Bally et al in "Encapsulation of Antineoplastic Agents in Liposomes (US Patent 5,736,155, issued 7 April 1998, entire document).

Claims 1 and 10 are as described above and are rendered obvious over Bepler et al or Osaki et al, in view of Saxon et al for the reasons given above.

Claim 15 specifies within Claim 10 that the first and second therapeutic agents are co-encapsulated in the same delivery vehicle.

While Bepler et al or Osaki et al in view of Saxon et al render obvious methods of testing drugs or combinations of drugs on cells which are representative of a specific patients phenotype for preparation of pharmaceutical compositions comprising first and second therapeutic agents which are stably associated with a first and second "delivery vehicle", Bepler et al, Osaki et al and Saxon et al fail to explicitly teach that the drug combinations are "co-encapsulated" in the same delivery vehicle.

Bally et al teach drug combinations that are co-encapsulated.

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It would have been obvious for one of ordinary skill in the art to prepare a pharmaceutical composition comprising an optimized combination of therapeutic agents using co-encapsulated stably associated delivery vehicles to administer the agents because Bally et al discloses that co-encapsulation was successfully used and routine.

One of ordinary skill in the art would have been motivated to employ co-encapsulated therapeutic agents because Bally discloses that co-encapsulation provides pharmacokinetic benefits.

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the use of the co-encapsulation for the purpose of delivering combination therapeutic agents was routinely practiced at the time of Applicants invention.

In view of the foregoing, the method of claim 15, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC §103(a).

### ***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine S. Hibbert whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully submitted,

Catherine S. Hibbert  
Examiner/AU1636

/ Christopher S. F. Low /  
Supervisory Patent Examiner, Art Unit 1636